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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,964	12/07/2001	David T. Curiel	D6384	1873

7590 10/16/2003

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	6

DATE MAILED: 10/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,964	CURIEL ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Non-Final Rejection

Claims 1-14 are pending examination.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

The use of the trademark PERKIN-ELMER (page 21) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

The use of the trademark AMERICAN TYPE CULTURE COLLECTION (pages 20 and 42) has been noted in this application.

The use of the trademark BOEHRINGER INGELHEIM (page 42) has been noted in this application.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Claim Objections

Claims 5, 12 and 13 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Herpes thymidine kinase gene, cytosine deaminase and purine nucleoside phosphorylase gene are not toxins genes. Ricin is considered a toxin. Merriam-Webster Dictionary defines "toxin" as a poisonous substance that is a specific product of the metabolic activities of a living organism and is usually very unstable, notably toxic when introduced into the tissues, and typically capable of inducing antibody formation. The genes are merely enzymes that can convert a suicide substrate to a toxic product.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14, as best understood, are readable on a genus of a promoter of a gene with undetectable expression in liver, wherein the genus of a

promoter of a gene is not claimed in a specific biochemical or molecule structure that could be envisioned by one skilled in the art at the time the invention was made.

The specification contemplates a genus of a promoter of a gene with undetectable expression in liver (page 5, lines 16-20). The specification has possession of two variations of the cyclooxygenase-2 (COX-2) promoter, COX-2 L (-1432/+59) and COX-2 M (-833/+59) that display reduced expression in the liver. However, the specification does not provide sufficient description of a genus of a promoter of a gene with undetectable expression in liver. The specification does not provide sufficient description for the structure (essential nucleotides) of the COX-2 promoter that is required for observing an undetectable expression in the liver. The specification does not describe how to make a representative number of promoters with undetectable expression in liver. The specification teaches that there is variation of expression in tissues between the COX-2 L and COX-2 M (page 37) and does not disclose a relationship between the structure of COX-2 and a genus of a promoter with undetectable expression in liver. The art of record is absent that the disclosed COX-2 promoter had a known structural relationship to a genus of a promoter with undetectable expression in liver. It is not apparent that on the basis of the applicants' disclosure an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the claimed invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of a promoter that must exhibit the disclosed biological functions as contemplated by the specification.

It is not sufficient to support the present claimed invention directed to a genus of a promoter of a gene with undetectable expression in liver. The claimed invention as a whole is

not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of a promoter of a gene with undetectable expression in liver that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a promoter of a gene that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Furthermore, claims 2, 3, 10, and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims are rejected under 35 U.S.C. 112, first paragraph, because there is no description of the two COX-2 promoters due to improper incorporation of essential subject matter. Possession is necessary but not sufficient to

satisfy written description. See Enzo Biochem, Inc. v.Gen-Probe, Inc., 296 F.3d 1316, 1330, 63 USPQ2d 1609, 1617 (Fed. Cir. 2002).

The attempt to incorporate essential subject matter (COX-2M and COX-2L promoters) into this application by reference to Inoue et al., J. Biol Chem 270:24965-24971, 1995 and Inoue et al., FEBS Lett 350:51-54, 1994 is improper because the specification does not indicate where the cyclooxygenase L (-143/+59) and cyclooxygenase-2 M (-833/+59) are found in the journal articles. The two COX-2 promoters are considered essential material for the application. In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application. See MPEP 608.01(p).

As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one**

sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application). (Emphasis added.)

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, since the claimed invention is not supported by a sufficient description (for possessing a genus of a promoter of a gene with undetectable expression in liver) as recited in the claims, particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the invention as broadly claimed so that it would operate as intended, *e.g.*, to make an adenoviral vector comprising a toxin gene operably linked to a promoter of a gene with undetectable expression in liver for use in a method of cancer gene therapy comprising the adenoviral that has reduced expression of said toxin gene in liver cells.

With respect to claims embracing a genus of a promoter with undetectable expression in liver and COX-2 promoter, the specification does not teach one skilled in the art how to make and/or use the claimed invention for the reasons set forth under the 112 first paragraph written description rejection. It is acknowledged that the written description and the enablement rejection are separate rejections under 112 first paragraph, however, the reasons for the 112 enablement rejection are the same reasons set forth in the written description rejection.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence

or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to a method of killing tumors cells with reduced liver toxicity in an individual comprising administering an adenoviral vector comprising a toxin gene operably linked to a promoter of a gene with undetectable expression in liver. The invention lies in the field of *in vivo* cancer gene therapy.

Furthermore, and with respect to claims directed to any vector useful for gene therapy and directed to any treatment of an animal; the state of the art exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several

major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

In further view of the doubts expressed above by Anderson and Verma, the state of the art at the time the application was filed and currently for cancer gene therapy as discussed by Vile et al., (*Gene Therapy*, Vol. 7, pp. 2-8, 2000). Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. None the less, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).
>
> A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor

from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).

Therefore, in view of the art of record, a method of killing tumor cells using cancer gene therapy was considered highly unpredictable.

The as-filed specification provides several working examples (pages) that will be briefly discussed herein: Example 3 describes using two different lengths promoters (cox-2L and cox-2M) derived from phPES2 were placed in front of each transgene for selective expression. Example 5 describes that in vivo analysis of the cox-2 promoters in adenoviral constructs in major organs. Example 6 describes in vivo analysis of luciferase expression using cox-2 promoters in an adenoviral construct in subcutaneous tumors in athymic nude mice. Example 8 describes toxicities studies using adenoviral comprising the Cox-2 promoter. Examples 9 and 10 describe killing pancreatic carcinoma *in vitro* using an adenoviral vector comprising either a COX-2M or COX-2L promoter operably linked to a toxin gene. The specification does not provide a working example of the claimed method.

In view of the In re Wands Factors, the as-filed specification does not provides sufficient guidance and/or evidence for one skilled in the art to make and/or use the claimed invention. In view of the breadth of the term "administering", the specification does not provide sufficient guidance for practicing the claimed method without an undue amount of experimentation. Therefore, in view of concerns set forth above and by the art of record [See Vile, Anderson, Verma], the as-filed specification does not provide sufficient guidance for how to reasonably correlate from luciferase studies to the claimed method.

Furthermore with respect to delivering an adenoviral vector in the claimed methods using any route of delivery, it would take one skilled in the art an undue amount of experimentation to

determine what route of administration (*e.g.* intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) other than direct administration would result in killing tumor cells using the adenoviral vector comprising a toxin gene operably linked to a COX-2 promoter. The art of record for the route of administration for gene therapy as exemplified by Verma, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). The unpredictability for targeting an adenoviral vector to a specific cell *in vivo* using any route of administration are further supported by Vile (*supra*); Reynolds et al., (Gene Therapy, Vol. 6, 1999, pages 1336-1339) and Dmitriev et al., (Journal of Virology, Vol. 72, 1998, pages 9706-9713). In view of the art of record and the lack of guidance provided by the specification for overcoming the problems with adenoviral vector delivery, it is not apparent to one skilled in the art how to reasonably extrapolate from direct administration to any route of administration to treat a brain tumor in any individual.

Furthermore, with respect to claims 7, 8, 9, 10 11, 12, and 14, the claims are directed to killing tumor cells using an adenoviral vector comprising a promoter operably linked to a toxin gene. However, the genes embrace by the claims are not toxin genes, they are merely enzymes that can act as a suicide substrate to a toxic product. Merriam-Webster Dictionary defines "toxin" as a poisonous substance that is a specific product of the metabolic activities of a living organism and is usually very unstable, notably toxic when introduced into the tissues, and typically capable of inducing antibody formation. In addition, the toxin genes are not toxic,

unless the suicide substrate is present in the cells with the gene. The specification teaches how to kill tumor cells by delivering an adenoviral vector comprising a herpes thymidine kinase gene, cytosine deaminase and purine nucleoside phosphorylase gene in the presence of a corresponding suicide substrate. The specification does not teach how to kill tumor cells using an adenoviral vector comprising a herpes thymidine kinase gene, cytosine deaminase and purine nucleoside phosphorylase gene without a suicide substrate. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

In view of the concerns set forth by the art of record, the as-filed specification does not reasonably address the concerns put forth by the art of record for cancer gene therapy for killing tumor cells in an individual and using any route of administration. As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed methods generate a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid therapy method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the art of record at the time the invention was made do not provide sufficient guidance and/or evidence to reasonably enable one skilled in the art to practice the claimed invention. Given that cancer gene therapy wherein any adenoviral vector is employed to kill tumor cells in any individual was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any adenoviral vector cited in the claims, one skilled in the art

would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability of gene therapy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 3 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: how –1432/+59 and –833/+59 correspond to the nucleotide sequence of a cyclooxygenase promoter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4, 5, 7, 9, 12, and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Sorscher et al. (US Patent 6,017,896) as evident by Brookes et al., The Prostate, Vol. 36, pages 18-26, 1998). Sorscher teaches an adenoviral vector comprising the PNP gene under the regulatory control of the human probasin promoter used for killing tumor cells, including pancreatic cancer cells (column 14, lines 29-31 and column 45, lines 25-45). Sorscher teaches using HSV thymidine kinase gene followed by ganciclovir for killing tumor cells or cytosine deaminase (column 1, line 47- column2, line 54). Sorscher does not specifically teach that the probasin promoter has undetectable expression in liver.

Brookes teaches that the probasin promoter showed very low to negligible activity in HepG2 cells (page 22). Thus, Sorscher as evident by Brookes teaches an adenoviral vector comprising a toxin gene operably linked to a promoter of a gene with undetectable expression in liver.

Claims 1, 4, 5, 7, 9, 12, and 13 under 35 U.S.C. 102(a) as being anticipated by Adachi et al. (Cancer Research, Vol. 60, pages 4305-4310, August 2000). Adachi teaches an adenoviral vector comprising a luciferase reporter gene or herpes simplex thymidine kinase gene under control of the human MK promoter (pages 4305-4306). Adachi teaches that the human MK promoter gene has high activity in tumor cell lines (Wilm's tumor G-401, colon cancer LS174T, and Burkitt's lymphoma Daudi cell lines) and low activity in the liver (pages 430506). Adachi teaches that the adenoviral vector can be used in a method of suicide gene therapy (page 4308).

Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by Yamamoto et al. (IDS, Gastroenterology, Vol. 118, April 2000, abstract 1003) as evident by Babincova et al. (Life

and Medical Sciences Online,

http://www.itrust.de/lamso/lpext.dll.Infobase0?title0003.htm?fn=docu 8/7/2000, pp. 1-4).

Yamamoto teaches an adenoviral vector comprising a COX-2 promoter operably linked to a luciferase gene. Yamamoto does not specifically teach that a luciferase is a toxin gene.

Babincova teaches using the luciferase gene to destroy neoplastic cells. Thus, the adenoviral taught by Yamamoto as evident by Babincova would anticipate the claimed adenoviral vector.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 7, 9, 10, 11, 12, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al. (IDS, Gastroenterology, Vol. 118, April 2000, abstract 1003) taken with Woo (IDS, US Patent 6,217,860).

Yamamoto teaches an adenoviral vector comprising a COX-2 promoter operably linked to a luciferase gene. Yamamoto teaches that the adenoviral vector comprising a COX-2 promoter can be used for adenoviral gene therapy against colon cancer liver metastasis. However, Yamamoto does not teach using a toxin gene selected from the group consisting of herpes simplex virus thymidine kinase gene and the cytosine deaminase gene in the adenoviral vector.

However, at the time the invention was made, Woo teaches an adenoviral vector comprising a herpes simplex virus thymidine kinase gene or cytosine deaminase gene operably linked to a promoter to destroy tumor cells (abstract, column 1, lines 22-45 and column 6, lines 20-47).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine of teaching of Yamamoto taken with Woo namely to produce an adenoviral vector comprising a COX-2 promoter operably linked to a toxin gene selected from the group consisting of herpes simplex virus thymidine kinase gene and the

cytosine deaminase gene. One of ordinary skill in the art would have been motivated to use either toxin gene because both toxin genes are well known in the art for killing tumor cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 6, 7, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorscher et al. (US Patent 6,017,896) taken with Dmitriev et al., (Journal of Virology, Vol. 72, 1998, pages 9706-9713).

Sorscher teaches an adenoviral vector comprising the PNP gene under the regulatory control of the human probasin promoter used for killing tumor cells, including pancreatic cancer cells (column 14, lines 29-31 and column 45, lines 25-45). Sorscher teaches using HSV thymidine kinase gene followed by ganciclovir for killing tumor cells or cytosine deaminase (column 1, line 47- column2, line 54). However, Sorscher does not teach using a RGD motif in the HI loop of the adenovirus fiber protein in the adenoviral vector.

However, at the time the invention was made, Dmitriev teaches that incorporating the RGD motif in an adenoviral vector improve the ability of the vector to transduce several types of cells, which are normally refractory to adenovirus infection (page 9207).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Sorscher taken with Dmitriev, namely to produce an adenoviral vector comprising a COX-2 promoter operably linked to a toxin gene, wherein the adenoviral vector further comprises a RGD motif in the HI loop of the adenovirus fiber protein. One of ordinary skill in the art would have been motivated to use a RGD motif in

the HI of the adenovirus fiber protein in the adenoviral vector to increase the tropism of the adenoviral vector.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER